THE WESTERN
Journal of Medicine

Refer to: Brasher C, Siegler RL: The hemolytic-uremic syndrome.
West J Med 134:193-197, Mar 1981

The Hemolytic-Uremic Syndrome

CRAIG BRASHER, MD, *and* RICHARD L. SIEGLER, MD, *Salt Lake City*

Our experience with 61 episodes of the hemolytic-uremic syndrome in 60 patients showed a mean patient age of 3 years and a higher incidence of the disease during the summer months. Diarrhea, often bloody, preceded the other features of the illness in 93 percent of the cases. Hemolytic anemia, hematuria and proteinuria occurred in all of the patients. Thrombocytopenia and severe azotemia (blood urea nitrogen greater than 100 mg per dl) occurred in 74 percent and 72 percent of the children, respectively. Blood transfusions were necessary in 64 percent and dialysis was required in 54 percent of the cases. Mortality was low (5 percent) and 85 percent of the children had a complete recovery.

THE HEMOLYTIC-UREMIC SYNDROME (HUS) is the most frequent cause of acute renal failure in infants and young children. Its features, which include microangiopathic hemolytic anemia, thrombocytopenia and acute nephropathy, have been described extensively in recent series and reviews.[1-5] While the pathogenesis remains uncertain, a variety of infectious agents may damage the renal vascular endothelium and initiate the coagulation cascade. This in turn traps platelets in the kidney, causes mechanical fragmentation of the erythrocytes and produces acute renal failure.

This report describes our experience with 61 episodes of HUS in 60 patients who were admitted to the Primary Children's Medical Center or the University of Utah Medical Center between October 1970 and January 1979. Except for five children from Montana, Oregon, Colorado and Nevada, they all resided in either Utah or Idaho. While three patients cared for during the early 1970's received heparin, none of the others received anticoagulant, antithrombotic or fibrinolytic agents.

From the Division of Pediatric Nephrology, Department of Pediatrics, University of Utah College of Medicine, Salt Lake City.

Submitted, revised, September 2, 1980.

Reprint requests to: Richard L. Siegler, MD, Department of Pediatrics, University of Utah College of Medicine, 50 North Medical Drive, Salt Lake City, UT 84132.

Patients

The average age of our patients was 3 years (range 5 months to 12½ years); 85 percent of the children were younger than 5 years old and 37 percent were between the ages 1 and 2 years (Figure 1).

We detected a seasonal variation, with half of the cases occurring during the summer months (Figure 2).

Prodrome

Almost all the children had diarrhea (93 percent), vomiting (90 percent), or both (84 percent), which preceded the detection of anemia and renal disease by about a week (Table 1). The diarrhea was bloody in about half of the cases, and two patients were referred because ulcerative

ABBREVIATIONS USED IN TEXT
BUN=blood urea nitrogen
CNS=central nervous system
HUS=hemolytic-uremic syndrome

colitis was suspected. Abdominal pain often accompanied the diarrhea, and one patient underwent an appendectomy for suspected acute appendicitis.

A decrease in urinary output was noted by the parents in about half of the children, and pallor or fever was reported during the prodrome in 34 percent and 25 percent of the patients, respectively. While 23 percent of the children had an upper respiratory infection (URI) during the prodrome, its high frequency in the general pediatric population makes an assessment of any causal relationship difficult. In approximately 15 percent of the cases, a seizure preceded admission.

Results

Laboratory Values

All of our patients had proteinuria and hematuria on admission (Table 2). Almost all of them became severely anemic with a hematocrit of less than 25 percent developing in 97 percent; in 85 percent of the children hematocrits were less than 20 percent. Evidence of microangiopathy on blood smears (schistocytes, burr cells) was noted in all cases. Because transfusions were given for hematocrits approximating 15 percent, the potential maximum severity of the anemia could not be estimated. While 75 percent of the children had platelet counts below 100,000 per cu mm, only 10 percent had severe thrombocytopenia (less than 20,000 per cu mm).

Severe azotemia (blood urea nitrogen [BUN] greater than 100 mg per dl) occurred in 72 percent of the cases, and hyperkalemia was common during the oliguric phase (43 percent). Conversely, hypokalemia occurred frequently during the recovery (diuretic) phase (51 percent). Serum uric acid levels exceeded 20 mg per dl in 43 percent of the 23 patients tested.

Clinical Course

In 39 of the children (64 percent) oliguria (less than 240 ml per m^2 per day) developed. In 34 of these 39 anuria (less than 15 ml per day) occurred (Table 3). The mean duration of the anuria was 5.2 days (range 1 to 17), and the combined anuria-oliguria was 8.6 days (range 1 to 23). Dialysis, usually peritoneal, was carried out in 54 percent of the patients. Hypertension was present in 51 percent of the children, and usually occurred only briefly during the first few days in hospital. Late-onset hypertension was infrequent, but was often a presage of severe chronic hypertension. Sixty-four percent of our patients required one or more transfusions with packed

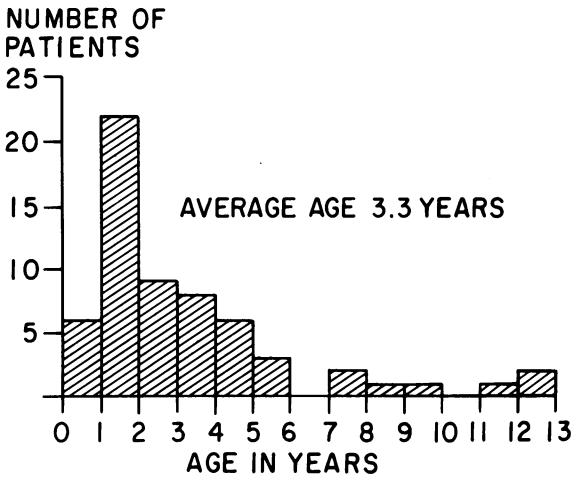

Figure 1.—Age distribution of 60 patients (61 episodes) with hemolytic-uremic syndrome.

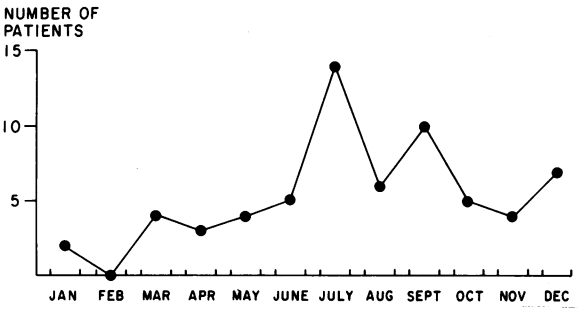

Figure 2.—Seasonal variation in incidence of 61 episodes of hemolytic-uremic syndrome.

TABLE 1.—*Clinical Prodromes Before Admission to Hospital in 60 Patients (61 Episodes) With Hemolytic-Uremic Syndrome*

Prodromes	*Number (Total 61)*	*Percent*
Diarrhea	57	93
With blood	30	49
Vomiting	55	90
Vomiting and diarrhea	51	84
Oliguria-anuria	29	48
Pallor	21	34
Fever	15	25
Upper respiratory infection	14	23
Seizure	9	15

erythrocytes. Seizures occurred during the acute phase of the illness in 24 (40 percent) of the children. However, they were usually generalized and brief, and rarely recurred.

Outcome

Only two patients (3 percent) died during the acute phase of the disease. One other child died two years later, after an unsuccessful renal transplant and chronic hemodialysis (Table 4). One child had a recurrence approximately three years after her first episode. Her initial episode resulted in brain damage and the second in severe chronic hypertension and mild chronic renal failure.

Chronic long-term sequelae were infrequent. Hypertension was still noted in three (5 percent) of the children, in two of them after a year and in a third after five years. Mild renal failure was still present in one of these children after five years. Chronic neurological sequelae (seizures, cortical blindness or psychomotor retardation) persisted in three children (5 percent) at 1, 1½ and 5 years, respectively. Overall, five of the long-term survivors (8 percent) have sustained one or more major sequelae. But, in that different sequelae occurred with recurrence of HUS in the one child, there were major sequelae following six disease episodes in these five patients. One additional child has persistent proteinuria (1+ to 2+), but no other abnormal features. Considering the three children (5 percent) who died, 85 percent of the total number of patients are alive and well with normal values for analysis of urine, blood pressure and renal function, and an absence of neurological abnormalities.

TABLE 2.—*Laboratory Values in 60 Patients (61 Episodes) With Hemolytic-Uremic Syndrome*

Laboratory Values	*Number/Total*	*Percent*
Proteinuria and hematuria	61/61	100
Hematocrit <25%	59/61	97
Hematocrit <20%	52/61	85
Platelet count <100,000 per cu mm	45/61	74
Platelet count < 20,000 per cu mm	6/61	10
BUN >100 mg/dl	44/61	72
K+ >6 mEq/L (oliguric phase)	26/61	43
K+ <3 mEq/L (diuretic phase)	31/61	51
Uric acid >20 mg/dl	10/23	43

BUN = blood urea nitrogen

TABLE 3.—*Clinical Course in 61 Episodes of Hemolytic-Uremic Syndrome*

Clinical Course	*Number (Total 61)*	*Percent*
Oliguria (<240 ml/m²/d)	39	64
Anuria (<15 ml/d)	34	56
Dialysis	33	54
Hypertension	31	51
Transfusion(s)	39	64
Seizure(s)	24	40

TABLE 4.—*Outcome in 61 Episodes of Hemolytic-Uremic Syndrome*

Outcome	*Number (Total 61)*	*Percent*
Deaths	3	5
Early	2	3
Late	1	2
Chronic hypertension	3	5
Chronic renal failure	1	2
Chronic neurological sequelae	3	5
Patients with one or more major sequelae	5	8

Discussion

HUS is not a rare disease, and it is responsible for almost all acute dialysis therapy on our pediatric service. While largely a pediatric disorder, it is also seen in adults, particularly in postpartum women and in women taking oral contraceptives.[2] Moreover, we have been seeing progressively more cases during the last few years, and during the year following this study, we cared for an additional 19 children. Whether this represents a true increase in incidence or merely greater physician awareness is uncertain.

As almost all patients share a common prodrome, the possibility of HUS should be considered in any young patient with diarrhea, especially if accompanied by bloody stools. A falling hematocrit, schistocytes, hematuria and proteinuria should facilitate early diagnosis and avoid injudicious fluid administration and subsequent edema, hyponatremia or both.

While convulsions occurred in 40 percent of our patients, they were not predictive of outcome or central nervous system (CNS) sequelae. Of the seizure episodes, 58 percent were associated with serum sodium concentrations of less than 130 mEq per liter and 13 percent with serum calcium levels of less than 8 mg per dl. There were no episodes of hypertensive encephalopathy. Details of our patients' CNS findings are being reported elsewhere.[6]

As there is good evidence that HUS is a localized intravascular coagulopathy,[2] it is not surprising that anticoagulant, antithrombotic, and fibrinolytic agents have all been used. While it has been suggested that heparin might be helpful,[2,7] there is little evidence of any clear-cut value.[8-11] Similarly, antithrombotic drugs (such as aspirin and dipy-

ridamole) and the fibrinolytic agent streptokinase, appear to be of unproved value or carry an unfavorable risk-benefit ratio.[1] Therefore, we have followed the widely accepted policy of supportive therapy while waiting for spontaneous recovery.[2,7,8]

Unless dehydration is present, fluids are restricted to ongoing losses (insensible, plus urinary and gastrointestinal losses). Because initially most children are essentially anuric, this amounts to 350 ml per m^2 of glucose water a day. If they are also hyponatremic, even less water is given.

Hyperkalemia (potassium greater than 6.0 mEq per liter) is treated with the oral or rectal administration of sodium polystyrene sulfonate (Kayexalate) in doses of 1 gram per kg of body weight. Only rarely are additional measures (such as bicarbonate, glucose with insulin, or calcium) necessary. Because half of our patients became hypokalemic during the recovery phase, we now give generous amounts of potassium once diuresis begins and serum potassium concentrations approach 3 mEq per liter.

Ordinarily, hypertension is easily controlled with intravenously given diazoxide (5 mg per kg of body weight per dose) or intramuscularly given hydralazine (0.2 mg per kg of body weight per dose).

Transfusions with packed erythrocytes (5 to 10 ml per kg of body weight) are generally reserved for children with hematocrits approaching 15 percent. Occasionally they are given earlier, if a gallop rhythm develops. High-output heart failure did not develop in any of the children in our series.

While dialysis has generally been recommended when anuria lasts for more than 24[1,2] or 48 hours,[9,11] we usually do not carry out this treatment in our patients until the BUN concentration exceeds 150 mg per dl, irrespective of the duration of the oliguria or anuria. Exceptions have included uncontrollable or severe hyperkalemia, severe fluid overload or acidosis, or progressive encephalopathy. By following these guidelines, there have been no deaths from a delay in initiating dialysis. Because of its technical simplicity, all but a few older children have been treated with peritoneal dialysis rather than hemodialysis. Peritoneal dialysis is continued for a maximum of 72 hours or until the BUN approaches 50 mg per dl. Most dialysis treatments have lasted between 24 and 48 hours. By withholding protein and only giving fats, carbohydrates and essential amino acids (Amin-Aid, McGaw Laboratories), diuresis almost always begins before the BUN again exceeds 150 mg per dl, and a second dialysis is needed only occasionally. But, because of fluid volume and electrolyte constraints, a negative caloric and nitrogen balance usually occurs in the children for a week or two. Earlier and more frequent dialysis would permit more normal caloric intake and better nutrition. But these advantages need to be weighed against the additional cost and potential morbidity of repeated dialysis. None of our patients have died of infection or any other complication of malnutrition, and mortality and recovery rates compare favorably with those from centers advocating early dialysis.[1,2,7,11]

Very high serum uric acid levels (greater than 20 mg per dl) were found in 43 percent of our patients during the oliguric phase of their illness. This phenomenon, which has previously been reported,[12] did not result in detectable gouty arthropathy or nephropathy, and was not treated with allopurinol.

All 22 patients who did not have oliguria recovered completely. Moreover, surprisingly, we found no difference in the duration of anuria between those who recovered and those left with chronic renal, neurological or hypertensive problems. There was a significant difference, however, (Student's t test, $P < 0.05$) between the number of days of combined anuria-oliguria in those who recovered (8.0 ± 5.5 [1 SD]) and those who sustained chronic renal failure or hypertension (15.3 ± 5.7). This difference, however, was not apparent in those left with only chronic neurological damage. In addition, while 29 of 35 patients (83 percent) with combined anuria-oliguria of 14 days or less recovered completely, only one of four (25 percent) with more prolonged renal failure escaped major sequelae. This relationship between duration of renal shutdown and recovery of renal function has also been noted by others.[4]

None of the 19 additional patients cared for during the year following this study have died; however, one sustained brain damage and another has mild hypertension. Thus, our overall experience indicates that with careful supportive therapy over 95 percent of the children with HUS will survive and approximately 90 percent of survivors will recover completely.

REFERENCES

1. Kaplan BS, Thomson PD, de Chadarevian JP: The hemolytic uremic syndrome. Pediatr Clin N Am 23:761-777, 1976

2. Goldstein MH, Churg J, Strauss L, et al: Hemolytic-uremic syndrome. Nephron 23:263-272, 1979

3. Riella MC, George CRP, Hickman RO, et al: Renal microangiopathy of the hemolytic-uremic syndrome in childhood. Nephron 17:188-203, 1976

4. Dolislager D, Tune B: The hemolytic-uremic syndrome. Am J Dis Child 132:55-58, 1978

5. Sorrenti LY, Lewy PR: The hemolytic-uremic syndrome. Am J Dis Child 132:59-62, 1978

6. Bale JF, Brasher C, Siegler RL: The central nervous system manifestations of the hemolytic-uremic syndrome: Relationship to metabolic alterations and prognosis. Am J Dis Child 134:869-872, 1980

7. Lieberman E: Hemolytic-uremic syndrome. J Pediatr 80:1-16, 1972

8. Kaplan BS, Katz J, Krawitz S, et al: An analysis of the results of therapy in 67 cases of the hemolytic-uremic syndrome. J Pediatr 78:420-425, 1971

9. Gianantonio CA, Vitacco M, Mendilaharzu F, et al: The hemolytic-uremic syndrome. Nephron 11:174-192, 1973

10. Vitacco M, Avalos JS, Gianantonio CA: Heparin therapy in the hemolytic-uremic syndrome. J Pediatr 83:271-275, 1973

11. Upadhyaya K, Barwick K, Fishaut M, et al: The importance of nonrenal involvement in hemolytic-uremic syndrome. Pediatrics 65:115-120, 1980

12. Kaplan BS, Thomson PD: Hyperuricemia in the hemolytic-uremic syndrome. Am J Dis Child 130:854-856, 1976

Allergy and Man's Food History

SOME FOODS ARE more allergenic than others because of mankind's past. If you stop and think about it, prehistoric man has been shown to have been a roving creature that killed small animals, picked berries and dug up roots. He did not raise cows and milk them, he did not have fields of grain and he did not grow sugars. I think that the reason these foods are the most commonly allergenic foods is because they have entered man's diet more recently. Bread is not the staff of life; unfortunately it is in some ways probably one of the worst things going. I think probably one of man's worst discoveries was figuring out how to put yeast with grain. And of course, the growing of grain enabled us to discontinue our nomadic life and to settle in one spot. And by settling in one spot we developed inhalant allergies to the vegetation in the area. Then we grew grain and figured out how to mix the grain with yeast, and we got booze and bread; and we have never been the same since. Some patients just do better on what we call a caveman diet: meats, fruits and vegetables.

—JOHN H. BOYLES, Jr, MD, *Dayton, Ohio*

Extracted from *Audio-Digest Otorhinolaryngology*, Vol. 13, No. 14, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 E. Chevy Chase Drive, Glendale, CA 91206.